18. Torizo Takahashi and Juichiro Shibasaki: Syntheses of Heterocyclic Compounds of Nitrogen. LXXXII*. Phenyl Pyridyl Ethers. (7)**.

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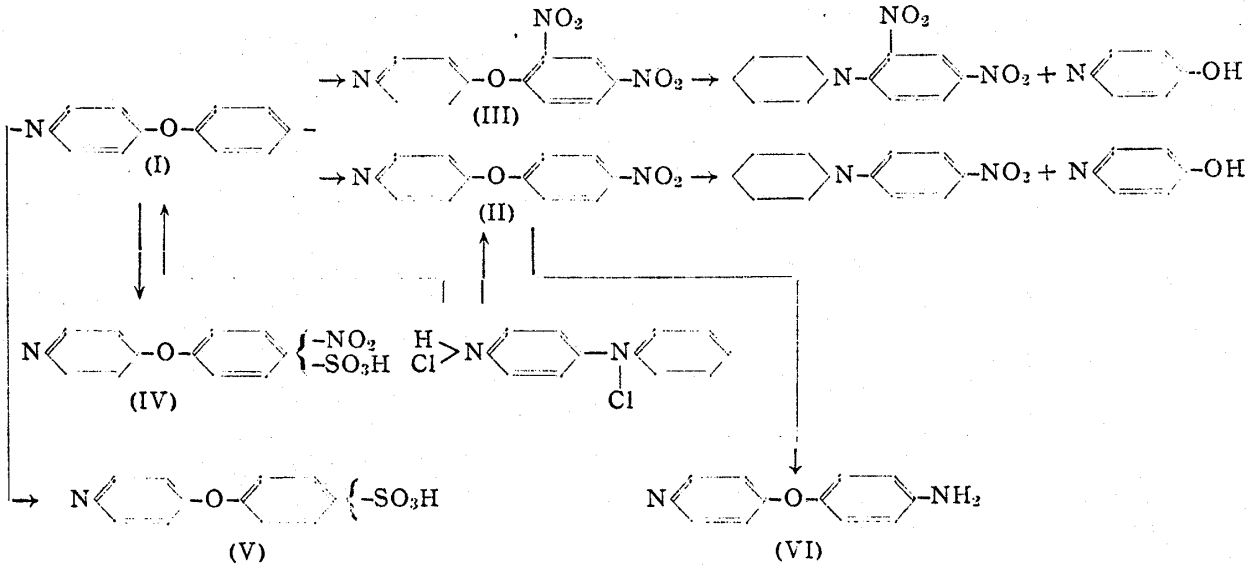
In one[1] of the previous papers, we reported on the nitration of phenyl pyridyl-(2) ether. This time, we examined other two isomers of phenyl pyridyl ethers, namely phenyl pyridyl-(3) ether and phenyl pyridyl-(4) ether, and the results are described in this paper.

Nitration of phenyl pyridyl-(4) ether Phenyl pyridyl-(4) ether (I) was prepared by the same method as that of Koenigs and his collaborator[2], condensing 4-pyridyl pyridinium dichloride with potassium phenoxide in phenol as a solvent, and in the procedure, despite the reduction of the amount of phenol as a solvent to 3/5 of that reported by Koenigs, the same yield was still obtained. The nitration of (I) was conducted similarly to that of phenyl pyridyl-(2) ether.

At first, the reaction was observed under such conditions that are recorded as No. 1 in Table I and the raw material was recovered in 92% yield without obtaining nitrated compounds. The recovery of (I) was proved by its melting point (45~46°) and also by conversion into its methiodide[3], m.p. 227.5~228.5°. The reaction under conditions No. 2 gave 4-nitrophenyl pyridyl-(4') ether (II) in 91% yield, and by reaction No. 3, 2,4-dinitrophenyl pyridyl-(4') ether (III) and a substance, freely soluble in dilute alkaline solution, were obtained. The latter was found by analyses to be mononitrophenyl pyridyl-(4') ether monosulfonic acid (IV) in which some parts of (I) was replaced by a nitro group and a sulfonic acid group, and no further investigation relative to the positions of these two substituted groups was made. On the other hand, a mixture of (II) and (III) was produced by lowering the temperature from 55~60° to 15~20° in the condition No. 3. (I) was treated with concentrated sulfuric acid at 45~50° and phenyl pyridyl-(4) ether monosulfonic acid (V) was prepared, whose position of the sulfonic acid group was not determined.



* Report LXXX: J. Pharm. Soc. Japan, 72, 1492 (1952). Report LXXXI: J. Pharm. Soc. Japan, 73, 219 (1953).

** Part (6): J. Pharm. Soc. Japan, 72, 1141 (1952).

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1) Takahashi, Shibasaki: J. Pharm. Soc. Japan, 72, 1137 (1952).
2) Koenigs, Greiner: Ber., 64, 1049 (1931).
3) Renshaw, Conn: J. Am. Chem. Soc., 59, 297 (1937).

To determine the structures, (II) and (III) were converted into methiodides, and 4-nitrophenylpiperidine[4] and 2,4-dinitrophenylpiperidine[4] were prepared by the action of piperidine on (II) and (III), respectively, the latter method being the same as that employed in the previous paper[1]. It was confirmed that the resultant mononitro compound by the nitration of (I) is (II) which was prepared by condensation of 4-pyridyl pyridinium dichloride with potassium salt of 4-nitrophenol in 4-nitrophenol as a solvent. In addition, the nitrated compound (II) was changed by reduction to 4-aminophenylpyridyl-(4') ether (VI).

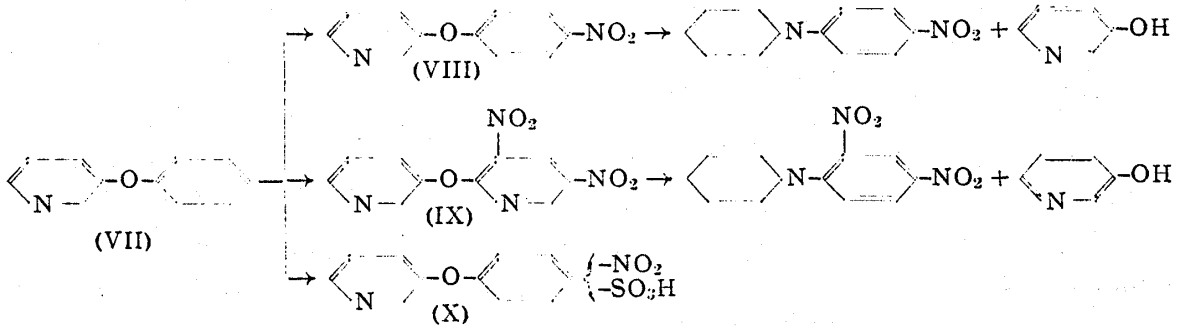
TABLE I Nitrating Conditions for Phenyl Pyridyl-(4) Ether

No.	Material (I) g	Solvent (cc.)	HNO_3 (d=1.38)g.	Reaction temp.°C	Reaction time hrs.	Yield of (II) %	Yield of (III) %	Yield of (IV) %	(I) recovered%
1	0.5	CH_3COOH 10	0.35	85~90	2	—	—	—	92
2	2	conc.H_2SO_4 32	1.4	0~5	2	91	—	—	—
3	2	conc.H_2SO_4 32	4.2	55~60	2	—	48.5	32	—

Nitration of phenyl pyridyl-(3) ether By the diazotization of 3-aminopyridine[5], which was prepared by the Hofmann degradation of nicotinamide, 3-iodopyridine[6] was formed which was condensed with potassium phenoxide to (VII), applying the method of Renshaw and his co-worker[3].

The first reaction was observed under conditions No. 1 in Table II and the starting material was recovered in 90% yield with no nitrated compound. The recovered oily material was proved to be (VII) as a picrate and its methiodide was found difficult to crystallize, because it was hygroscopic, though it was described as crystals by Renshaw. Secondly the reaction under conditions No. 2 gave a nitrated compound melting at 90~127°, and repeated recrystallizations did not give a substance having a sharp melting point. The nitrated compounds dissolved in benzene were run through a column containing alumina and developed with benzene. The fractions eluting at first included 4-nitrophenyl pyridyl-(3') ether (VIII), m.p. 108~110°, and from the latter fractions, 2,4-dinitrophenyl pyridyl-(3') ether (IX), m.p. 129~132° was obtained. By the reaction No. 3 besides (IX) was produced a substance, freely soluble in dilute alkaline solution, which was sure to be a derivative of (VII) containing a nitro group and a sulfonic acid group, namely mononitrophenyl pyridyl-(3') ether monosulfonic acid (X), but the positions of these two substituted groups were not determined.

The structures of (VIII) and (IX) were determined through the facts that respective treatment of (VIII) and (IX) with piperidine yielded 4-nitrophenylpiperidine[4] and 2,4-dinitrophenylpiperidine[4] from a portion insoluble in caustic alkali solution, and 3-hydroxypyridine[7] from a caustic alkali-soluble portion. Meanwhile, an attempt to form (VIII) by condensation of 3-iodopyridine with potassium salt of 4-nitrophenol failed.



4) Lellman, Geller: Ber., **21**, 2281 (1888).
5) Gilman: Org. Syntheses, **30**, 3 (1950).
6) Räth: Ann., **486**, 101 (1931).
7) Blau: Monatsh., **6**, 651 (1885); Weidel, Murmann: Monatsh., **16**, 749 (1895).

TABLE II Nitrating Conditions for Phenyl Pyridyl-(3) Ether

No.	Material (VII) g.	Solvent (cc.)	HNO_3 (d=1.38)g.	Reaction temp.°C	Reaction time hrs.	Yield of (VIII)%	Yield of (IX) %	Yield of (X) %	(VII)recovered %
1	0.5	CH_3COOH 8	0.35	85~90	2	—	—	—	90
2	0.5	conc. H_2SO_4 12	0.35	−5~−7	0.5	9.5	9	—	—
3	0.5	conc. H_2SO_4 8	0.70	3~6	2	—	46	18.5	—

Survey of the Results. Summarizing the results of the present work and of the previous one[1], the following facts were revealed.

The nitrations of 3 isomers of phenyl pyridyl-(2), -(3), and -(4) ethers, resulted in the recovery of the starting materials when using acetic acid as a solvent, and in case of sulfuric acid as a solvent, the replacement occured at 2- and 4-positions of the benzene nucleus and the pyridine nucleus remained unattacked. From these results, it may probably be explained that by the influence of +M effect of the oxygen atom on the benzene nucleus, 2- and 4-positions are activated against the attack of electrophilic reagents.

The comparison of nitrating temperatures of phenyl pyridyl ethers for the production of 4-nitro and 2,4-dinitro derivatives are given in Table III. It shows that the ease of the nitration increases in the order of phenyl pyridyl-(2), -(4), and -(3) ethers.

TABLE III Comparison of Nitrating Temperatures of Phenyl Pyridyl Ethers

Nitro derivative obtained	Temp. for -(3) ether	Temp. for -(4) ether	Temp. for -(2) ether
4-Nitrophenyl derivative	−5~−7 °C	0~5 °C	30~35 °C
2, 4-Dinitrophenyl derivative	−5~−7	15~20	45~50

We gratefully acknowledge the assistance of Mr. M. Uchibayashi and Mr. Y. Tanaka in this work.

Experimental

4-Nitrophenyl pyridyl-(4′) ether (II)—i) Two g. of phenyl pyridyl-(4) ether (I) was dissolved in 32 cc. of sulfuric acid (Bé 66°), by cooling with ice and salt. To the solution was added, with stirring, 1.4 g. nitric acid (d=1.38) keeping the temperature between −5° and 0°. Stirring was continued for another 2 hours at that temperature, after the addition was complete. The reaction mixture was then poured into cold water, made alkaline with 20% sodium hydroxide solution, and extracted with ether. After being dried over sodium sulfate, the ether was distilled off and the residue soon solidified. Recrystallization from petroleum ether yielded 2.3 g. of colorless scales, m.p. 79~81°, which showed no depression of melting point when mixed with the product of (ii). *Anal.* Calcd. for $C_{11}H_8O_3N_2$: C, 61.11; H, 3.70; N, 12.96. Found: C, 61.16; H, 3.95; N, 13.28. This nitration corresponds to No. 2 in Table I.

ii) A mixture of 5 g. of 4-pyridyl pyridinum dichloride, 5.6 g. of potassium salt of 4-nitrophenol, and 17.5 g. of 4-nitrophenol was well mixed and heated at 180~200° in an oil bath for 4 hours, all components melting at about 120°. The cooled mixture was made strongly alkaline with 20% sodium hydroxide solution and extracted several times with ether. The ethereal solution was dried over sodium sulfate and evaporated. The residue (1.7 g.) was recrystallized from petroleum ether to colorless scales, m.p. 80~81°.

Methiodide of (II)—A mixture of 0.2 g. of (II) and 0.5 g. of methyl iodide was heated for an hour on a boiling water bath. The cooled crystalline substance was washed with ether and dried (0.31 g.). Recrystallization from ethanol gave yellow plates, m.p. 207~209°. *Anal.* Calcd. for $C_{12}H_{11}O_3N_2I$: N, 7.82. Found: N, 8.21.

Reaction of (II) with piperidine—In a sealed tube 0.05 g. of (II) and 0.2 g. of piperidine were placed and heated at 170~180° for 3 hours. To the cooled, red mixture was added dilute acetic acid and the crude product (0.035 g.) was separated. Recrystallization from ethanol yielded yellow scales, m.p. 104~105°. The melting point of the substance did not depress when fused with 4-nitrophenylpiperidine.

2,4-Dinitrophenyl pyridyl-(4′) ether (III) and mononitrophenyl pyridyl-(4) ether monosulfonic Acid (IV)—Two g. of (I), 32 cc. of sulfuric acid (Bé 66°), and 4.2 g. of nitric acid (d=1.38) were treated in a similar way, as in (i) of 4-nitrophenyl pyridyl-(4′) ether at 55~60°. The reaction mixture was poured into cold water and the crystals (1.18 g.) were separated. After recrystallization from water, pale yellow pillars freely soluble in dilute alkaline solution, were obtained, which decomposed at 283~284° with softening at about 260°. The results of analyses indicated

that it coincided with mononitrophenyl pyridyl-(4) ether monosulfonic acid (IV), containing one molecule of water of crystallization. *Anal.* Calcd. for $C_{11}H_8O_6N_2S \cdot H_2O$: C, 42.04; H, 3.19; N, 8.92; S, 10.19. Found: C, 41.84; H, 3.44; N, 8.73; S, 10.54.

The mother liquor, separated from crystals (IV), was basified with 20% sodium hydroxide solution and extracted with ether. After being dried over sodium sulfate, the solvent was removed. Recrystallization from ether gave 1.48 g. of colorless prisms, m.p. 92～94.5°. *Anal.* Calcd. for $C_{11}H_7O_5N_3$: C, 50.75; H, 2.69; N, 16.15. Found: C, 50.99; H, 3.28; N, 16.29. This nitration correspounds to No. 3 in Table I.

Methiodide of (III)—A mixture of 0.1 g. of (III) and 0.5 g. of methyl iodide was treated in a similar way to that of methiodide of (II). Recrystallization of the crude product (0.14 g.) gave yellow needles, m.p. 156°. *Anal.* Calcd. for $C_{12}H_{10}O_5N_3I$: N, 10.42. Found: N, 10.46.

Reaction of (III) with piperidine—A mixture of 0.2 g. of (III) and 0.5 g. of piperidine was heated on a boiling water bath for 15 minutes, by which it soon turned red with rising of temperature, and diluted acetic acid was added to the reaction mixture. The precipitate was filtered, dried (0.14 g.) and recrystallized from ethanol. The yellow scales, m.p. 90～92°, obtained were proved to be 2,4-dinitrophenylpiperidine by the mixed melting point determination.

Phenyl pyridyl-(4) ether monosulfonic acid (V)—One g. of (I) was dissolved in 16 cc. of sulfuric acid (Bé 66°) and heated for 2 hours at 40～45° with stirring. The reaction mixture was then poured into cold water, and made slightly alkaline with 20% sodium hydroxide solution. The solution was concentrated to approximately 20 cc. and crystals of sodium sulfate were removed while still warm. From the cooled mother liquor, colorless needles were separated, to which dilute hydrochloric acid was added to make slightly acidic and the precipitates were extracted with methanol for separating sodium chloride. The methanol was removed, the residue was recrystallized repeatedly from methanol, and colorless needles (1.3 g.) were obtained which decomposed at about 290° with softening at around 110°. The product was positive for the sulfur test. *Anal.* Calcd. for $C_{11}H_9O_4NS$: C, 52.59; H, 3.59; N, 5.58. Found: C, 52.55; H, 3.84; N, 5.22.

4-Aminophenyl pyridyl-(4′) ether (VI)—To 2.2 g. of stannous chloride, dissolved in 5 cc. of 35% hydrochloric acid, was slowly added 0.5 g. of (II) and the temperature rose. The mixture was heated on a boiling water bath for an hour and evaporated to dryness under a reduced pressure. The residue was made strongly alkaline with 30% sodium hydroxide solution and extracted with ether. The ethereal solution was dried over sodium sulfate, evaporated, and the crude product (0.29 g.) was recrystallized from ether to colorless needles, m.p. 160～162°. *Anal.* Calcd. for $C_{11}H_{10}ON_2$: N, 15.05. Found: N, 14.46.

Picrate of phenyl pyridyl-(3) ether—It was prepared by the usual method. The yellow precipitate was collected and purified from ethanol to yellow needles, m.p. 130～132°. *Anal.* Calcd. for $C_{11}H_9ON \cdot C_6H_3O_7N_3$: N, 14.00. Found: N, 13.92.

4-Nitrophenyl pyridyl-(3′) ether (VIII) and 2,4-dinitrophenyl pyridyl-(3′) ether (IX)—Half a gram of (VII) was dissolved in 8 cc. of sulfuric acid (Bé 66°) with cooling in an ice bath. To the solution was slowly added, with stirring, a mixture of 0.35 g. of nitric acid (d=1.38) and 4 cc. of sulfuric acid, keeping the temperature at −7 to −10°. After the addition was complete, the mixture was kept stirring for 30 minutes at that temperature and then poured into cold water, which was made strongly alkaline with 20% sodium hydroxide solution and extracted with ether. The ethereal solution, dried over sodium sulfate, was evaporated and a solid was soon formed. The product (0.25 g.) which dissolved in benzene, was run through a column containing active alumina and developed with benzene. Then it was found that (VIII) eluted at first and following fractions contained (IX). Recrystallization of (VIII) from diluted methanol yielded 0.06 g. of colorless needles, m.p. 108～110°. *Anal.* Calcd. for $C_{11}H_8O_3N_2$: C, 61.11; H, 3.70; N, 12.96. Found: C, 61.40; H, 3.78; N, 13.18. Recrystallization of (IX) from methanol gave 0.07 g. of colorless prisms, m.p. 129～132°. *Anal.* Calcd. for $C_{11}H_7O_5N_3$: C, 50.75; H, 2.69; N, 16.15. Found: C, 50.55; H, 2.91; N, 16.47. This nitration corresponds to No. 2 in Table II.

Reaction of (VIII) with piperidine—A mixture of 0.03 g. of (VIII) and 0.1 g. of piperidine was treated in a similar way to that of the reaction of (II) with piperidine, and yellow scales, m.p. 103～105°, were obtained. No melting point depression was observed when mixed with 4-nitrophenylpiperidine.

Reaction of (IX) with piperidine—To 0.12 g. of (IX) was added 0.5 g. of piperidine and the mixture was heated on a boiling water bath for 15 minutes, by which it soon turned red with rising of temperature, extracted with ether, and the ethereal solution was shaken with 10% sodium hydroxide solution. The ethereal layer was dried over sodium sulfate, and evaporated. The residue was recrystallized from ethanol and formed yellow scales (0.05 g.), m.p. 90～92°. It was found identical with 2,4-dinitrophenylpiperidine. The alkaline layer, which was separated from the ethereal layer, was neutralized with dilute acetic acid and evaporated to dryness. The residue was extracted with hot benzene. The crude product, obtained by distillation of the solvent, was recrystallized from benzene to colorless needles, m.p. 126～128°. The melting point coincided with

that found in the literature[7]).

2,4-Dinitrophenyl pyridyl-(3′) ether (IX) and mononitrophenyl pyridyl-(3′) ether monosulfonic acid (X)—Half a gram of (VII), 8 cc. of sulfuric acid (Bé 66°), and 0.7 g. of nitric acid (d= 1.38) were treated in a similar way to that of (i) of 4-nitrophenyl pyridyl-(4′) ether, but at 3~6°. The crude product, obtained from the ethereal solution, was recrystallized from methanol to colorless prisms (0.35 g.), m.p. 129~132°, which gave no depression on admixture with (IX) mentioned above. From the alkaline solution, which was separated from the ethereal solution, crystals precipitated, which were collected and made slightly acidic with dilute hydrochloric acid. The substance was recrystallized repeatedly from water to pale yellow needles, m.p. ca. 275° (decomp.), which was positive for the sulfur test and was identical with mononitrophenyl pyridyl-(3) ether monosulfonic acid according to the results of analyses. *Anal.* Calcd. for $C_{11}H_8O_6N_2S$: C, 44.59; H, 2.70; N, 9.46. Found: C, 45.34; H, 3.12; N, 9.88. This nitration corresponds to No. 3 in Table II.

Summary

The nitrations of phenyl pyridyl-(3) ether and phenyl pyridyl-(4) ether were carried out. The nitrations, applying concentrated nitric acid and acetic acid at 85~90°, resulted in the recovery of the raw materials with no nitrated compound. The nitrations with concentrated nitric acid and concentrated sulfuric acid, at a low temperature, resulted in 4-nitro- and 2,4-dinitrophenyl pyridyl ethers, and at high temperature, 2,4-dinitrophenyl pyridyl ether and mononitrophenyl derivatives containing a sulfonic acid group. In addition, by the treatment of phenyl pyridyl-(4) ether with concentrated sulfuric acid at 45~50°, a monosulfonic acid derivative of the starting material was obtained.

(Received November 27, 1952)